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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

1. (Original) A method of promoting neurogenesis comprising the step of:

administering a therapeutic amount of a nitric oxide donor compound to a patient in need of neurogenesis promotion.

2. (Original) A compound for promoting neurogenesis comprising an effective amount of a nitric oxide donor sufficient to promote neurogenesis.

3. (Original) A neurogenesis promoter comprising a nitric oxide donor in a pharmaceutically acceptable carrier.

4. (Original) The neurogenesis promoter according to claim 3, wherein said nitric oxide donor augments nitric oxide in a tissue.

5. (Original) The neurogenesis promoter according to claim 4, wherein said nitric oxide donor is selected from the group consisting essentially of phosphodiesterase inhibitors, and L-arginine.

6. (Original) A method of augmenting the production of neurons by administering an effective amount of a nitric oxide donor to a site in need of augmentation.

7. (Amended) A method of increasing neurological function by administering an effective amount of a nitric oxide donor to a patient in need of increased neurological function.

8. (Amended) A method of increasing cognitive and neurological function by administering an effective amount of a nitric oxide donor compound to a patient in need of increased neurological function.

REMARKS

Claims 1-8 remain in the application. Claims 1-3 and 6-8 are in independent form.

Claims 7 and 8 stand objected to because of informalities in the claims. The Office Action states that the recitation of the treatment of individuals "in need" without the inclusion of a certain condition is incorrect. Claims 7 and 8 have been amended to more specifically recite that the patients are in need of increased neurological function and reconsideration of the objection is respectfully requested.

Claims 1-8 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the nitric oxide donors listed on page 5, paragraph 1 of the instant specification does not reasonably provide enablement for all nitric oxide donors. However, it is respectfully requested that since Applicants have included a variety of nitric oxide donors listed on page 5, this is indicative of a class of compounds and as such broad coverage for the class of compounds as is recited in the pending claims can be provided. Since the specification provides numerous examples of nitric oxide donors, the specification does enable the broad classification of nitric oxide donors as presently claimed and reconsideration of the rejection is respectfully requested. It at least claims those nitric oxide donors functionally related to the class functionalities claimed. Absent a showing that there are others outside of the claimed class, it is respectfully submitted that a prima facia showing is not presented.

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Moskowitz patent. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by the Moskowitz patent, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

The Office Action states that the Moskowitz patent teaches a method of treating strokes and the resulting neurological damage by administering nitric oxide releasing compounds. The therapeutic target of the Moskowitz approach is the reduction of cerebral infarction (i.e. volume of dead brain tissue) after ischemic stroke that is stroke caused by a lack of blood flow to the brain. Moskowitz seeks to increase blood flow to the brain to limit volume of infarction. In other words, the patent discloses treating injured brain in an attempt to salvage brain tissue. Further, the treatment of the Moskowitz patent is limited to times early after ischemic stroke when blood flow increase can reduce the volume of the damaged tissue. In the Moskowitz patent, the reduction of the infarction is mediated by administration of a substrate for NO before or early (within the first 1-2 hours) after stroke. The substrate is given from 16 hours before stroke to 2 hours after stroke. This enhances blood flow to the brain and thereby counteracts some of the loss of blood flow initiated by the stroke. The Moskowitz patent states in column 1 line 31 that, "the nervous system lacks the ability to regenerate," in column 1 lines 40- 44, "the ultimate size of the infarct which forms the basis of medical therapy is the extent of vascular support." Thus, according to the Moskowitz patent, the intervention must be designed to improve blood flow and thereby to reduce the ischemic lesion, because when the lesion is complete and cannot be reduced by treatment there is no benefit.

Additionally, the Moskowitz patent discloses that brain cannot regenerate. The data presented in the Moskowitz patent only relate to treatment of a model of ischemic stroke with a substrate of NO. All data presented by Moskowitz show a reduction of

volume of cerebral infarction, dilation of blood vessels, and as noted in column 3 line 18, the approach of the Moskowitz patent is to "limit the extent of stroke-associated infarct." The patent discloses that treatment should preferably begin shortly after the initiation of stroke and preferably at any point in time prior to the completion of the infarction process.

In contradistinction, the presently pending independent claims claim NO donors, PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on the volume of infarction. As disclosed throughout the currently pending patent application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the treatment. Further the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy is designed to be given days and weeks after the injury, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, at 24 or more hours after stroke. The presently pending independent claims claim inducing brain remodeling, an event that is independent of the reduction of the volume of cerebral infarction. There is no connection or association of reduction of volume of cerebral infarction with the production of new brain cells. There is no requirement of the presence of a NO donor to induce brain remodeling and functional benefit. Since the Moskowitz patent does not disclose or suggest the method and compound of the presently pending independent claims, the claims are patentable over the Moskowitz patent, and reconsideration of the rejection is respectfully requested.

Claim 6 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Bredt et al. reference. Reconsideration of the rejection under 35 U.S.C. §103(a) over the Bredt et al. reference, as applied to the claims is also respectfully requested.

It is Hornbook Law that before two or more references may be combined to negative patentability of a claimed invention, at least one of the references must teach or suggest the benefits to be obtained by the combination. This statement of law was first set forth in the landmark case of Ex parte McCullom, 204 O.G. 1346; 1914 C.D. 70. This decision was rendered by Assistant Commissioner Newton upon appeal from the Examiner-in-Chief and dealt with the matter of combination of references. Since then many courts have over the years affirmed this doctrine.

The applicable law was more recently restated by the Court of Appeals for the Federal Circuit in the case of ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572,1577, 221 U.S.P.Q. 929 (Fed. Cir. 1984). In this case the Court stated, on page 933, as follows:

> Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under Section 103 teachings of references can be combined only if there is some suggestion or incentive to do so. The prior art of record fails to provide any such suggestion or incentive. Accordingly we hold that the court below erred as a matter of law in concluding that the claimed invention would have been obvious to one of ordinary skill in the art under section 103.

This Doctrine was even more recently reaffirmed by the CAFC in Ashland Oil, Inc. v. Delta Resins and Refractories, Inc., et al., 776 F.2d 281,297, 227 U.S.P.Q. 657,667. As stated, the District Court concluded:

> Obviousness, however, cannot be established by combining the teachings of the prior art to produce the claimed invention unless there was some teaching, suggestion, or incentive in this prior art which would have made such a combination appropriate.

The Court cited ACS Hospital Systems, Inc. in support of its ruling. This Doctrine was reaffirmed in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995).

The Office Action states that the Bredt et al. reference teaches that nitric oxide is a diffusible multifunctional second messenger that has been implicated in numerous physiological functions in mammals ranging from dilation of blood vessels to immune response and potentiation of synaptic transmission. However, when read more specifically, there is no disclosure in the Bredt et al. reference for the potentiation of synaptic transmission. What is disclosed is that nitric oxide influences neurotransmitter release. Data is described on page 185 showing that NOS inhibitors block the release of neurotransmitters. There is no disclosure that the potentiation of synaptic transmission is related to synaptogenesis. The effect of NO on the release of neurotransmitters is not associated in any way with synaptogenesis. Synaptogenesis is the formation of new synapses, new connections in the growth and extension of synaptic and dendritic structures. The structural change of neurons is unrelated to the potentiation of neurons to release chemicals associated in electrical communications (i.e., neurotransmitters). Thus, NO as a neurotransmitter or a modulator of neurotransmission is distinct from NO as a promoter of synaptogenesis and one function is not related to the other. Further, the fact that NO has been implicated in numerous physiological and pathophysiological functions (i.e., cell death as extensively discussed on page 187-191 of the Bredt et al. reference) does not imply that NO is involved in brain plasticity and the production of new neurons, blood vessels, or synapses. There is no suggestion or teaching in the Bredt et al. reference of the ability of NO to induce functional improvement in brain plasticity after stoke or neural injury. Thus, the Bredt et al. reference does not disclose or suggest the invention as claimed in the presently pending independent claims, and as such the presently pending independent claims are patentable over the Bredt et al. reference and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Angel Webb